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"Hadrons in Radiation Therapy: Rationale, Achievements and Expectations"

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Hadrons (protons, neutrons, heavy ions) in radiation therapy: rationale, achievements and expectations

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Introduction

Radiation therapy plays an important role in cancer management. With the different techniques available today, i.e. surgery, radiation therapy, chemotherapy and eventually immunotherapy, about 45 % of all cancer patients can be cured **(Table I) [1]**. Radiation therapy contributes to the cure of 23 % of all cancer patients, alone (12 %) or in combination with surgery (6 %) or chemotherapy (5%). Thus, about half of the cancer patients who are cured received radiation therapy at least for part of their treatment.

Sixty five percent of the cancer patients are presenting at the first consultation with a localized tumour. Among these 65 %, about 1/3 fail (i.e., 25 % of the total number of cancer patients). This situation has to be improved mainly by "local" treatments, i.e., radiation therapy and/or surgery. It is the challenge, for the coming years, for teams involved in development of new radiation therapy modalities. Besides increasing the "cure rate", it is also important to improve the tolerance to the treatment and reduce the long term sequelae. Also palliative treatments deserve attention for those patients for which there is no hope of radical cure.

Experience accumulated in radiation oncology over a century indicates that all major improvements in the efficiency of the treatments were associated with, or made possible by, significant progress in technology.

The major steps involved were the move from 200 kV x rays to cobalt-60 and then to modern linacs providing x-rays beams of about 20 MV (and electrons when needed for some patients). Improvements in the beam qualities were often

combined with improvements in beam delivery systems, e.g. isocentric gantries, variable collimators, and later multileaf collimators, etc. In addition, these improvements were associated with significant progress in optimising dose distributions and in improving important related disciplines (e.g., imaging) which play roles in diagnosis and treatment.

Since the beginning of radiation therapy, radiation oncologists have always been concerned with new types of beams (different from conventional x-rays) in order to improve the efficacy of radiation therapy. This goal could be achieved through different approaches[2]:

(1) improving the physical selectivity of the therapeutic irradiations by using beams with better physical characteristics (penetration, collimation, etc.). It is the rationale for proton beam therapy. No radiobiological advantage is expected.

(2) applying different radiation qualities in order to improve the (radiobiological) differential effect between the cancer and normal cell populations.

Introduction of fast neutrons aimed at improving the radiobiological differential effect; no benefit was expected from the physical selectivity. However, a physical selectivity as least as good as that of conventional photon beams would in principle be needed.

(3) a combination of these two approaches: it is the goal of heavy ions.

The benefit of the physical characteristics and radiation qualities of the new beams needs to be evaluated by comparison with conventional high-energy photons. The vast majority of the patients are actually treated with photons, which are, and will remain, the reference radiation quality for the foreseeable future.

The reference radiation quality

A difficulty which arises when making these comparisons is the fact that the efficacy of photon therapy, against which the relative merits of the new beams have to be evaluated, improves continuously.

One of the most promising recent developments in photon beam therapy is "conformal" therapy, where all parameters are optimized to match as closely as possible the "treated volume" and the Planning Target Volume (PTV) i.e., the conformity index must be as close as possible to unity [3][4]. Different technical approaches are used to reach this goal, among them, intensity modulated radiation therapy (IMRT). In addition, support of the latest developments in 3-D treatment planning and imaging are required.

However, it is recognized that when optimising the treatment parameters to improve the conformity index in conformal therapy, other indexes can change adversely, e.g., the irradiated volume increases and the homogeneity throughout the PTV becomes worse.

This brings us to an important question: has the efficacy of photon beam therapy now reached a kind of plateau (at least as far as physical selectivity is concerned)? If this is the case, little additional clinical benefit can be expected from further technical improvements with photons, and one has to search for other beam qualities to improve the efficacy of radiation therapy (e.g., proton beams). This is an important point to consider, and about which there is no general consensus as yet.

Fast Neutron Therapy

Fast neutrons were the first "non-conventional" radiations to be used in therapy. The pioneering work in fast neutron therapy was performed by Stone and his associates at Berkeley between 1938 and 1943[**5**]. It was the first application of high-LET beams in therapy. In the late 1960s after extensive radiobiological experiments, a neutron therapy prgramme was initiated at the Hammermith Hospital in London, and a few years later in several centres in Europe and in the United States (see Chapter 11 in [**6**]).

Technological Aspects

Many centres, including 15 in Europe (former Soviet Union excluded) have applied fast neutron therapy using different types of generators, which can be schematically distributed into four groups:

- reactors, using the fast neutrons in the beam (limited application)
- "low-energy" cyclotrons, using mainly incident deuterons with energies ranging from 13 to 16 MeV (d+Be reaction);
- (d+T) generators;
- "high-energy" cyclotrons or linear accelerators (d/p+Be reaction)

Only for the fourth group can the physical selectivity and the technical conditions be considered to be sufficient (or nearly sufficient) for adequate treatments, especially in comparison with modern linear accelerators.

In some centres, large clinical programmes were completed from which important radiobiological and clinical conclusions could be derived. In some other centres, the facilities were shut down abruptly:

- in most centres, due to technical difficulties. For example, all (d+T) generators are now shut down.
- in other centres, due to patient recruitment problems.
- in general, due to "suboptimal" physical selectivity.

Today, in the majority of centres still active in neutron therapy, the technical conditions are becoming progressively comparable to those in modern photon beam therapy. In addition a few new high-energy facilities have been proposed (e.g., in China, Germany, Poland, Slovakia and South Africa).

Radiobiology

The radiobiological rationale for introducing high-LET (Linear Energy Transfer) radiations such as fast neutrons in cancer therapy is still valid and has not been contradicted by more recent radiobiological findings. The main arguments are :

-a reduction in the oxygen enhancement ratio (OER) with increasing LET;
-a reduction of the differences in radiosensitivity related to the position in the cell cycle (Figure 1) (chapter 11 in [6]);
-a reduction of the repair mechanisms and their clinical relevance.

However, these radiobiological arguments imply the need for the development of "predictive tests" allowing the radiation oncologist to select the best radiation quality (low- or high-LET) for a given patient group or individual patient.

Clinical aspects

The clinical results accumulated over more than 25 years, and in particular the conclusions of randomized trials, indicate that fast neutrons are definitely superior to photons for:

-locally extended, inoperable or recurrent salivary gland tumours;
-locally extended prostatic adenocarcinomas.

Salivary gland tumours

For inoperable primary or recurrent malignant salivary gland tumours, a randomized cooperative study was initiated in 1980 by the Radiation Therapy Oncology Group (RTOG) of USA and the Medical Research Council of Great Britain (MRC). At two years, there was a significant advantage for neutrons compared to photons for loco-regional control (76 vs 17 %, $P<0.005$) and a suggestive trend towards improved survival (62 vs 25 %). Ten year analysis continued to show a striking difference in loco-regional control (56 % for

neutrons vs 17 % for photons, P=0.009), but both groups experienced a high rate of metastatic failure: 7/12 for photons and 9/13 for neutrons **(Fig 2)[7]**.

In addition, several non-randomized studies confirmed the superiority of fast neutrons to achieve a high rate of loco-regional control in unresectable salivary gland tumours **(Table 2)[7][8]**. The average local control rate after neutron therapy is 65%; it ranges between 20 and 25% after conventional photon beam therapy.

As a conclusion, attempts at surgical resection of locally advanced salivary gland tumors should be limited to patients in whom there is a high likelihood of achieving clear margins. Neutron beam therapy should be considered as the treatment of choice in patients with unresectable salivary gland tumours or in patients where radical resection would require facial nerve sacrifice.

Prostatic adenocarcinomas

For prostatic adenocarcinomas, their typical slow growth rate and low cycling fraction provide a logical radiobiological rationale for exploring neutrons (high-LET) in the treatment of this disease.

In 1977, the Radiation Therapy Oncology Group (RTOG) carried out a randomized trial comparing "mixed beam" irradiation (a combination of photons and neutrons) to conventional photon irradiation for locally advanced prostatic cancer. The loco-regional control was significantly better after mixed-beam irradiation (at 10 years 70 % vs 58 %). The actuarial survival curves are also statistically different, favoring the mixed beam irradiation. The 5- and 10-year survivals after mixed beam irradiation are 70 and 46 % respectively, versus 53 and 29 % after photon beam therapy **(Fig. 3)[7]**.

Later on, in 1986, the Neutron Therapy Collaborative Working Group (NTCWG) initiated a second phase III trial, comparing neutrons (alone) and conventional photons. A significant difference ($P<0.01$) was observed in "clinical" loco-regional failure, with actuarial 5-year failure rates of 11 vs 32 % after neutrons and photons respectively **(Fig.4.a)[7]**. The corresponding "histological" failure rates (after biopsy) were 13 and 32 % respectively (P=001). In addition, 5-year post treatment PSA levels also showed an advantage to neutrons with 17 % of patients showing elevated PSA compared to 45 % for photon patients ($P<0.001$).

Survival rates at 5 years were not statistically significant. Due to the long natural history of recurrent prostate cancer, longer follow-up is required to assess the ultimate impact of the improved local control on survival. Neverthless, the differences in PSA levels could provide an indication. Late sequelae (mainly large bowel complications) were worse in the neutron treated group (11% vs 3 %).

However, an inverse correlation was found between major large bowel complications and collimation abilities of the neutron facility. No colostomy was required in 51 patients treated with a multileaf collimator at the University of Washington **(Fig.4.b)[7]**, while 6/38 patients from other centres required colostomy (movable jaw or fixed cone collimator).

Other studies also confirm the advantage of neutrons/high-LET radiations in the treatment of locally advanced protatic adenocarcinoma. In particular, the data from Louvain-la-Neuve (308 patients) suggest that mixed neutron-photon therapy is especially efficient in a subgoup of patients with unfavorable prognostic factors (PSA >20 ng/ml).

For other tumour sites or types, such as slowly growing soft tissue sarcomas, fixed lymph nodes in the cervival area, locally extended antrum tumours, and some bronchus carcinomas, the available clinical results tend to show a benefit with neutrons. However, this statement reflects a general clinical opinion from those who have personal experience with treating these tumours, but can not be considered as statistically significant or definitive because randomized trials have not been undertaken**[2][10][11]**

Proton beam therapy

The introduction of proton beams brought a significant improvement in physical selectivity. It is the most straightforward approach to improve the efficacy of therapeutic irradiations. In fact, one is impressed by the continuously increasing number of proton therapy centres in operation and by the number of projects under construction and proposed.

The first applications of proton beams took place in Berkeley in 1954. Today, proton beam therapy is applied in 20 centres worldwide, new facilities are in preparation (or under discussion), and more than 22,000 patients have been treated so far.

Technological aspects

Technical improvements have continuously been made, but an important change took place a few years ago, with the commercialisation of proton therapy equipment. In the past, proton therapy was performed with complex physics machines, adapted to clinical needs, not always available full-time, often expensive to maintain and difficult to tune.

Today commercial companies offer "turn key equipment" for proton therapy, adapted to the needs (or to the financial limitations) of the centre. A single company has received 5 or 6 firm orders to date. It is likely that this trend will

develop further. The establishment of the Northeast Proton Therapy Centre (NPTC) in Boston was obviously the trigger of the movement, but such a fast proliferation was certainly not expected.~~page~~

One can say in general that a new radiotherapy technique has gained its place among the other ones when the equipment can simply be purchased commercially. This is obviously now the case with proton therapy.

In addition to the "standard" proton therapy equipment, some centres (e.g., in Europe, the Paul Scherrer Institute, Villigen, Switzerland and the Med-AUSTRON project, Austria) have developed, or are planning to develop, highly sophisticated beam delivery systems exploiting all the potential advantages of the proton beams.

On the other hand, proton beams have no radiobiological advantages and a constant RBE (Relative Biological Effectiveness) with respect to photons of 1.0-1.1 is assumed. The vast clinical experience of photon therapy can be transferred directly to proton therapy.

Clinical aspects

Charged particle beams, and in particular protons, are ideal for treating intra-ocular lesions, since they can be made to deposit their absorbed dose in the target volume, while significantly limiting the irradiation of the non-involved ocular and orbital structures **(Fig 5)** (see chapter 11 in [6]).

Uveal melanomas

Large series of patients with uveal melanoma were treated with protons in several centres wordwide. MGH/HCL (Mass. General Hospital/Harvard Cyclotron Laboratory), in Boston, played a role of pioneer in the field **[12]**. Through September 1998, 2,568 uveal melanoma patients were treated.

Local control of the tumour within the treated eye was 96.3 + 1.5% and 95.4 + 3.3 % at 60 and 84 months, with 236 and 82 patients available for follow-up at those intervals, respectively. Two tumours recurred in the treated volume (70 Gy Eq), while 10 recurred at the margin the the treated volume. Survival at 5 years is about 80 %. proton treated patients survive at lest as well as patients treated primarily with enucleation.

Eye retention probability depends on tumour size, being 97 %, 93 %, and 78 % for patients with small, intermediate, and large tumpours, respectively. Significantly greater enucleation rates were observed in patients with large

tumours, with tumour height >8 mm, with tumour diameter >16 mm, and with tumour involvement of the ciliary body (P =<0.0001 for all comparisons).

Retinoblastoma

The physical selectivity of protons make them attractive for the treatment of retinoblastomas. Patients with the hereditary form of the disease are at high risk for developing a second primary malignacy. Proton techniques should reduce the risk of radio-induced tumour by reducing the volume of normal tissue irradiated. Absorbed doses of 40-60 Gy Eq in 23 fractions of 2 CGE are currently prescribed **[12]**.

Age-related macular degeneration

It is a leading cause of severe visual morbidity in countries like e.g. USA, where over 750,000 older citizens are afflicted. The prescribed doses range between 16 and 24 Gy Eq in 2 fractions, given on consecutive days **[12]**.

Tumours of the base of skull

Charged particle beams (e.g., protons) are ideal for treating skull base and cervical spine fumours: iradiation can be focussed in the target volume, while achieving significant sparing of the brain, brain stem, cervical cord, optical nerves and chiasma **[13].**

At MGH/HCL, in Boston, 621 patients with chordomas and low-grade chondrosarcomas (375 and 246 respectively) of the skull base and cervical spine (519 and 102 respectively) were treated with protons between 1975 and January 1998. For skull base tumour patients, with follow-up ranging fom 1 to 254 months (median 41 months), local recurrence fre survival is significantly better for chondrosarcomas than for chordomas: 98 % vs 73 % at 5 years and 94 % vs 54 % at 10 years respectively **(Figure 6.a)[13]**.

Male chordoma patients do better than do females: 81 % vs 65 % at 5 years and 65 % vs 42 % at 10 years. Overall survival is significantly better for chondrosarcoma than for chordoma patients: 91 % vs 80 % at 5 years and 88 % vs 54 % at 10 years respectively. For skull base chondrosarcoma patients, neither overall suvival nor recurrence free survival differed by gender.

For cervical spine tumours, with follow-up ranging from 1 to 172 months (median 36 months), local recurrence-free survival was not significantly different for chondrosarcomas and chordomas: 54 % vs 69 % at 5 years and 54 % vs 48 % at 10 years, respectively. There was also no significant difference in local

recurrence-free survival for males compared to females. The relationship between histology and overall survival in cervical spine tumour patients may be time dependent. At 5 years, overall survival for chondrosarcomas and chordomas were 48 % and 80 %, repectively, but at 10 years, were 48 % and 33 % respectively.

For recurrent patients, the benefit of salvage treatment is illustrated on **figure 6.b**. Salvage treatment consisted of subtotal tumour resection, gross tumour excision, radiation and/or chemotherapy. Survival at 2 and 5 years after salvage therapy was 63 % and 6 % respectively, compared to 21 % at 2 years for patients receiving supportive therapy only **[13]**.

CNS tumours in children

Pediatric tumours located in the CNS are particularly challenging and deserve highly refined techniques of radiation therapy like proton therapy **[14]**.

In Loma Linda, 28 children were treated with protons between 1991 and 1994, 16 with benign and 12 with malignant tumours of the CNS (54 Gy Eq). Three children died (gliomas), one has persistant disease, 4 presented with treatment-related toxicity (1 cataract, 2 hormonal failure, 2 seisures). All other children are doing well after a median follow-up of 25 months.

At MGH, 18 children with skull base-cervical spine chordomas were treated with protons at a dose of 69 Gy Eq (1.8 Gy Eq per fraction). At 5 years, actuarial survival and disease-free survival have been 68 and 63 % respectively. Cervical sites had a statistically worse prognosis. This rare tumour seems to behave in children as in adults. The first results from the Centre de Protonthérapie d'Orsay (CPO) confirm the excellent immediate and late tolerance **[14]**.

The results of proton beam therapy for other tumour types and localisations have been reported **[2][10]**. In the pioneering centres, patient selection, special care applied to each treatment, as well as expertise of the multi-disciplinary clinical teams, make it difficult to conclude whether the excellent results which were reported were due to the protons themselves or reflect the expertise of the respective teams.

Nevertheless, the pioneers were successful in bringing proton beam therapy from a "pioneer" level to the level of an "established" technique. The challenge for the next few years will be to confirm the initial results, on a larger scale and with better equipment.

However, for all the localizations for which protons were shown to be successful (although not in randomised trials), alternative techniques are promoted. For example, iodine-125 plaques are competing with protons in the treatment of uveal

melanomas. Prostate tumours were successfully treated with high-LET fast neutrons and heavy ions. Brachytherapy as well as conformal therapy with conventional photons also become more popular for prostate treatment. For tumours of the base of the skull, protons have to compete with the gamma knife and stereotactic x-ray techniques.

There are, however, some (rare) localizations for which the excellent physical selectivity of protons do not really allow for any competition: tumours adjacent to the spinal cord, tumours adjacent to or invading the brain stem and certain brain tumours (especially paediatric) as discussed above **(figure 7) [15].**

Pion Therapy

Between 1974 and 1994, 1100 patients were treated with negative pions at 3 centres. These particles, which provide a mixture of high- and low-LET components and some physical selectivity advantage, were very expensive to generate and the clinical results were unconvincing. All three facilities have now closed.

Heavy-Ion Beam Therapy

Heavy ions combine the advantages of the excellent physical selectivity of proton beams with the radiobiological advantages of fast neutrons for some types of tumours.

Rationale

The physical selectivity of heavy ions is even somewhat better compared to protons as far as penumbra and dose ratio between the SOBP (Spread Out Bragg Peak) and initial plateau are concerned. On the other hand, nuclear fragmentation of the beam particles is a disadvantage of heavy ions as energy is deposited beyond the primary Bragg peak. However, this aspect is probably not clinically significant as these light fragments are lower-LET particles.

More important is the fact that the RBE increases with increasing LET in depth, which improves the ratio of the "biological equivalent doses" between the SOBP and the initial plateau. In addition, high-LET radiation in the SOBP, makes heavy-ion beams specifically efficient against some malignant cells, such as hypoxic cells or cells in a resistant phase of the mitotic cycle. Furthermore, there is little repair possibility for cells irradiated in the SOBP. In contrast, the normal tissues irradiated at the level of the initial plateau, are exposed to relatively low-LET radiation and can thus benefit from repair mechanisms during fractionated irradiation.

The heavy-ion therapy programmes

The first heavy-ion therapy programme was initiated at Berkeley and 433 patients were treated between 1975 and 1992. The programme was limited by the availability of the machine and its complexity (which resulted in many unscheduled down times) and as consequence there was a patient recruitment problem. Nevertheless a great deal of valuable radiobiological and clinical information was obtained.

A summary of the clinical results obtained with neon ions in Berkeley is presented in **Table 3 [1]**. Some fast neutron therapy results are also presented. Although the recruitments are not comaparable, it should be pointed out that tumour types or sites for which an advantage was found with neon ions are those for which an advantage was also found with fast neutrons. This suggests a specific "high-LET" effect.

When the therapy facility was shut down at Berkeley, the NIRS (National Institute for Radiological Sciences) in Chiba, Japan started a programme with carbon ions. There was no limitation on machine time and it was thus possible to study common tumours on a large scale. A total number of 389 patients were treated between 1994 and February 1998.

In Europe, the first two patients were treated with carbon ions at the GSI (Gesellschaft für Schwerionenforschung), Darmstadt, Germany at the end of 1997. Difficult tumour localizations were selected for which full advantage could be taken of the scanning beam and the energy modulation system. There is, however, a strict limitation on machine time.

For the future, a heavy-ion therapy project at the German Cancer Research Center in Heidelberg is under discussion. This project will benefit from the experience gained at GSI.

In Austria, the MED-AUSTRON project is entering the feasibility study phase. The project proposes to combine the possibility of treating with either protons or carbon ions. It would of course be of great interest to be able to treat with low- and high-LET radiations in the same centre, under the same conditions, with proper selection of tumour characteristics and patient conditions.

Boron Neutron Capture Therapy (BNCT)

Only a short review of BNCT is presented here. The rationale for BNCT is to reach a physical selectivity at the cellular level **[16]**. Using thermal neutron beams, BNCT was started in the USA in 1951, at the Massachusetts Institute of

Technology (MIT) and at the Brookhaven National Laboratory (BNL). The clinical results were very poor. The technique was introduced in Japan by Hatanaka in 1968 and some promising results were obtained.

Today BNCT is applied using epithermal neutron beams in the USA at MIT and BNL; these programmes are supported by the Department of Energy. Forty patients were treated by the end of 1997. In Europe, the European Commission supports a BNCT programme in Petten, The Netherlands. Three patients were treated in 1997. The thermal neutron beam programme continues in Japan.

Today the only available sources of epithermal neutrons, with sufficient output, are nuclear reactors. However, construction of compact proton accelerators, producing epithermal neutrons of adequate energy (e.g. 2.5 MeV protons on a lithium target) has been envisaged.

The main expected advantage, is that such accelerator could be hospital based, and thus fractionation (of the irradiation and drug administration) could be optimized since the machine would be available 24 hours a day. In addition, patient positioning could be made easier and more accurate.

Lastly, BNCT is used today in combination with fast neutron therapy in some centres such as Seattle, Essen, and Orléans. Boron is incorporated in the tumour cells, and captures thermal neutrons produced in the body by the fast neutron beam.

Conclusion

Over the past decades, improvements observed in the results of radiation therapy have been linked mainly to technological developments. Indeed, in the sixties, definitely better clinical results were reported when 200 kV x-rays were progressively replaced by cobalt-60 and later on by high-energy linear accelerators. The physical selectivity of the irradiations were significantly improved.

Introduction of proton beams aims at further improving the physical selectivity of the irradiaton. The clinical results obtained by the pioneers in proton therapy, with physics machines, were sufficiently convincing to justify building and buying dedicated hospital based proton machines.

The benefit expected from the better physical selectivity of protons will have to be evaluated in comparison with conventional photon beam therapy, which remain the reference radiation therapy modality. When making this comparison, one has to be aware that new technology (e.g., conformal therapy, intensity modulated radiation theray, 3-D treatment planning) improves the efficacy of photons continuously.

Reaping the benefit expected from further improvement in the physical selectivity by using protons and/or conformal therapy is the challenge for the coming years.

The benefit of fast neutrons for some types of tumours is well established, in particular for slowly growing, well differentiated tumours. Randomized trials have shown their superiority, over conventional photons, for salivary gland tumours and prostatic adenocarcinomas. From a technical point of view, fast neutrons are applied today in the same conditions of safety, reliability and selectivity as photons.

Heavy ions combine the high physical selectivity of proton beams and the biological advantage of high-LET radiations for some tumour types. They appear today one of the most promizing radiation therapy modality at least for some tumour types and/or localizations. Patient selection between low- and high-LET radiations is essential and should be based on the tumour characteristics.

Finally, Boron Neutron Capture Therapy (BNCT) is still in an experimental phase. Although the rationale is particularly attractive, it is difficult today to draw conclusions from the available clinical data. However it is important for the future that protocols and results be reported and analysed applying the terminology, concepts and approaches currently in use for the other radiation therapy modalities.

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Table 1

Summary of the present situation concerning cancer cure rate		
		Cure rate
Patients presenting with localised tumour:	65%	
Cured by surgery		22%
Cured by radiotherapy		12%
Cured by combination of surgery and radiotherapy		6%
Patients presenting with inoperable or metastatic disease:	35%	
Cured by combined treatment including e.g., chemo- and immunotherapy	5%	
Total*	100%	45%

*excluding non melanoma skin cancers
(From Wambersie et al., EULIMA, 1992 [1]).

Table 2

Pooled European data of local control in advanced salivary gland tumours		
Reference	No of patients	Local control
Catterall (1987)	65	48 (74%)
Battermann and Mijnheer (1986)	32	21 (66%)
Duncan et al. (1987)	22	12 (55%)
Prott et al. (1996)	64	39 (61%)
Kovács et al. (1987)	15	13 (87%)
Krüll et al. (1995b)	74	44 (59%)
Skolyszweski et al. (1982)	3	2 (67%)
Overall	275	179 (65%)

(after Krüll et al. [8]).

Table 3

Summary of the clinical results obtained with high-LET radiations: fast neutrons and neon ions

Tumour site or type	Local control rates after	
	Fast neutrons (pooled data)	Neon ions Berkeley
Salivary gland tumours	67% (24%)	80% (28%)
Paranasal sinuses	67%	63% (21%)
Fixed cervical lymph nodes	69% (55%)	
Sarcomas	53% (38%)	45% (28%)
Prostatic adenocarcinoma	77% (31%)	100% (60-70%)
For comparison, the best estimates of local control rates currently obtained with conventional photon beam therapy are given in parentheses.		

From EULIMA Report, 1992 [1].

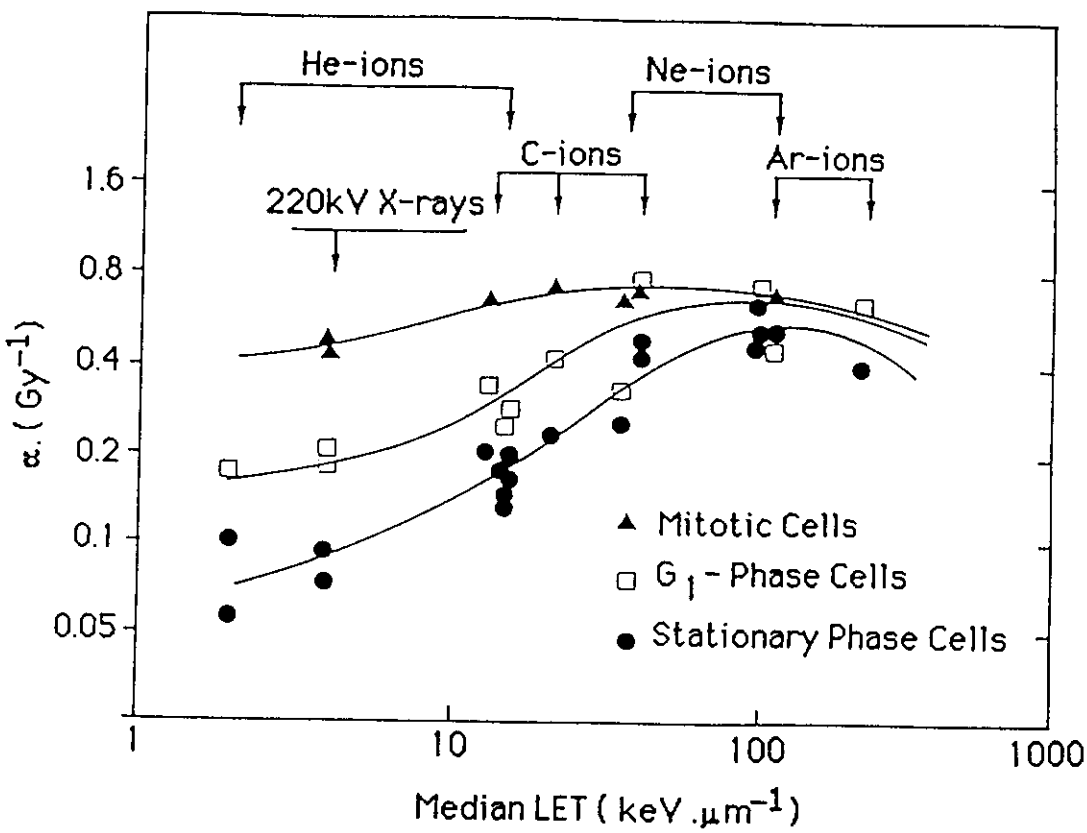


Figure 1

Differences in radiosensitivity with the position of the cells in the mitotic cycle. The differences are reduced when increasing LET.
Single-hit inactivation coefficients (α) for homogeneous populations of mitotic, G1-phase, and stationary phase Chinese hamster cells irradiated with 220 kV X-rays and various charged-particle beams, as a function of median LET (in keV/μm).

(From Chapman, cited in [6]).

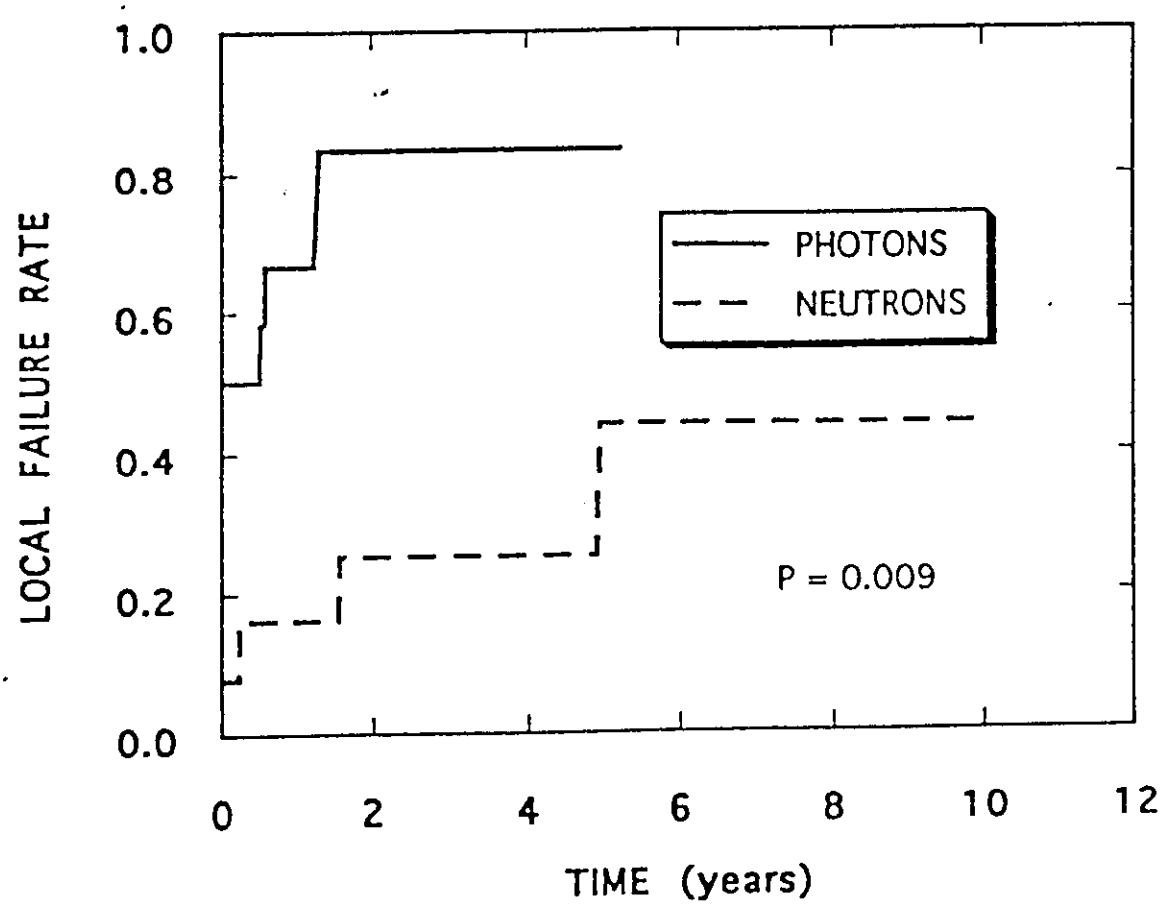


Figure 2

Neutron therapy of salivary gland tumours.

a. Probability of local-regional failure for unresectable salivary gland tumours. Starting values of the curves represent initial local–regional failure rates.
b. Actuarial survival for patients with unresectable salivary gland tumours.

(after Lindsley et al. [7]).

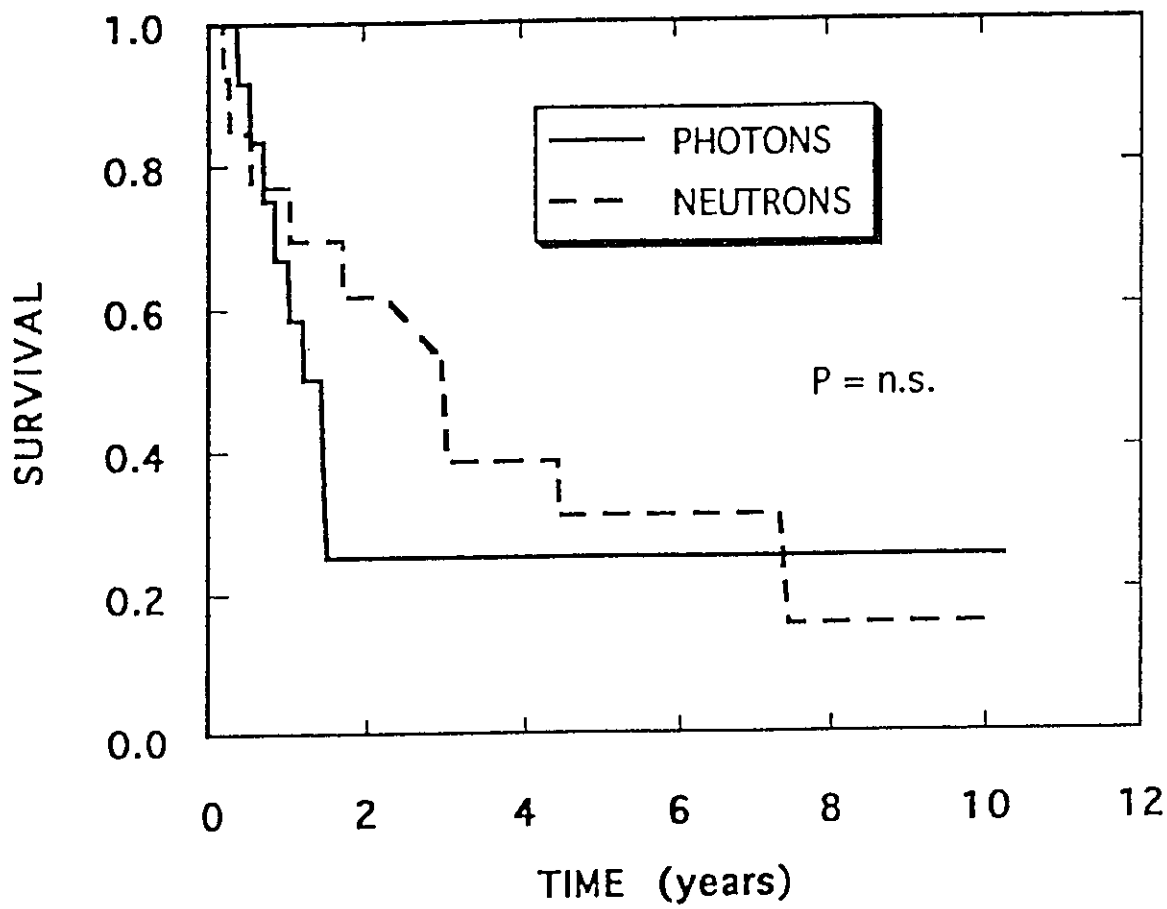

1.0
0.8
0.6
0.4
0.2
0.0
SURVIVAL
PHOTONS
NEUTRONS
P = n.s.
0
2
4
6
8
10
12
TIME (years)

Fig 2b

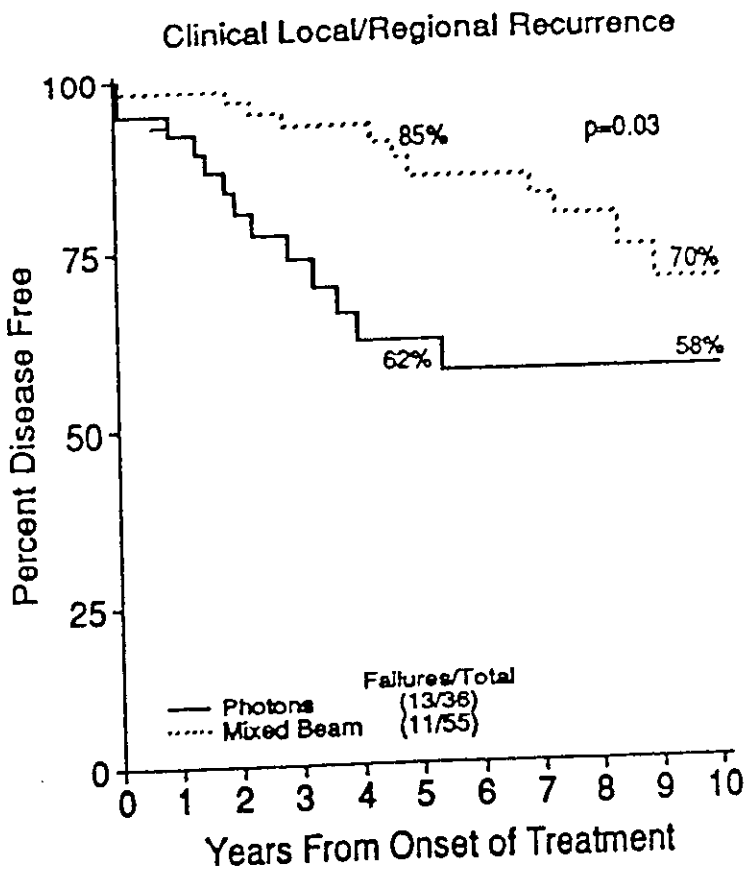


Figure 3

Loco-regional control and survival in patients treated with mixed (neutron/photon) beams or photons only (RTOG randomized trial) for locally extended prostatic adenocarcinoma.

a. Clinical local-regional control in patients with locally advanced prostate cancer.
b. Absolute survival of patients with locally advanced prostate cancer.

(from Lindsley et al., [7]).

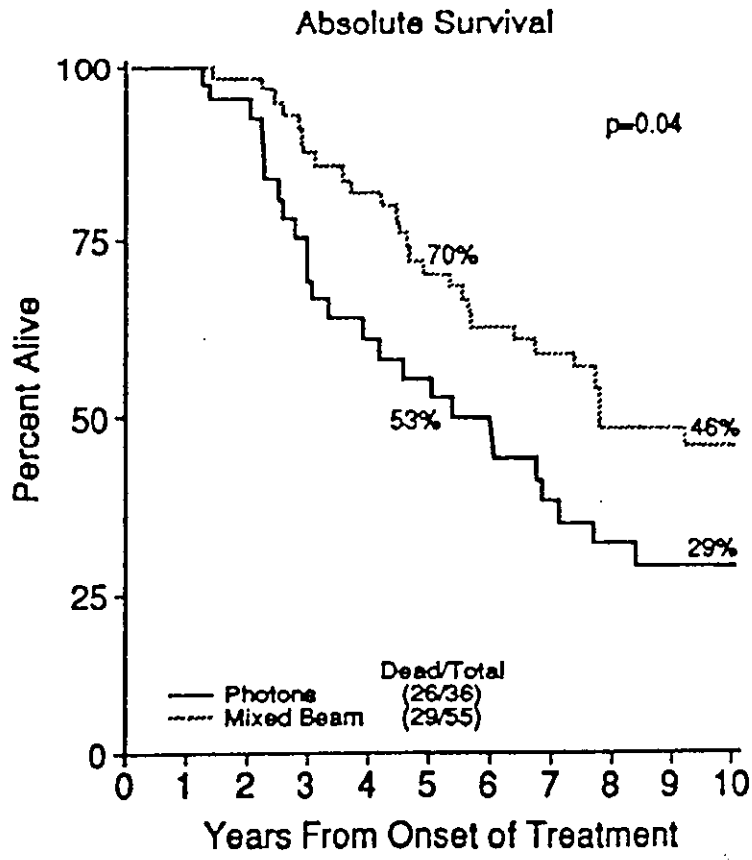

Absolute Survival
100
75
50
25
0
Percent Alive
p=0.04
70%
53%
46%
29%
Dead/Total
Photons (26/36)
Mixed Beam (29/55)
0 1 2 3 4 5 6 7 8 9 10
Years From Onset of Treatment

Fig 3b

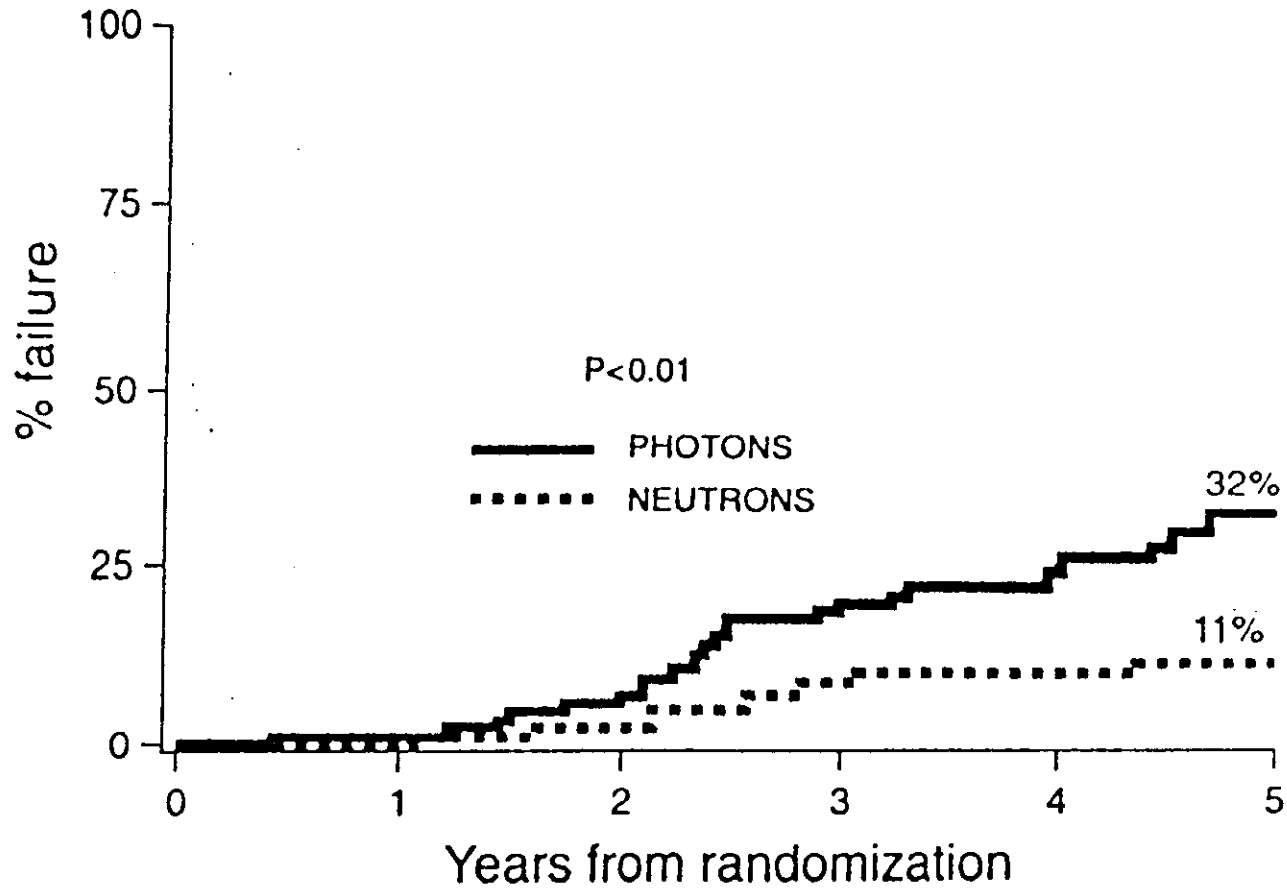


Figure 4

Results of NTCWG trial on prostate.

4.a Actuarial clinical loco-regional failure in patients with locally advanced prostate cancer.

4.a Cumulative incidence of major (≥ grade 3) complications in patients treated at the University of Washington with neutrons or photons.

(from Lindsley et al., [7]).

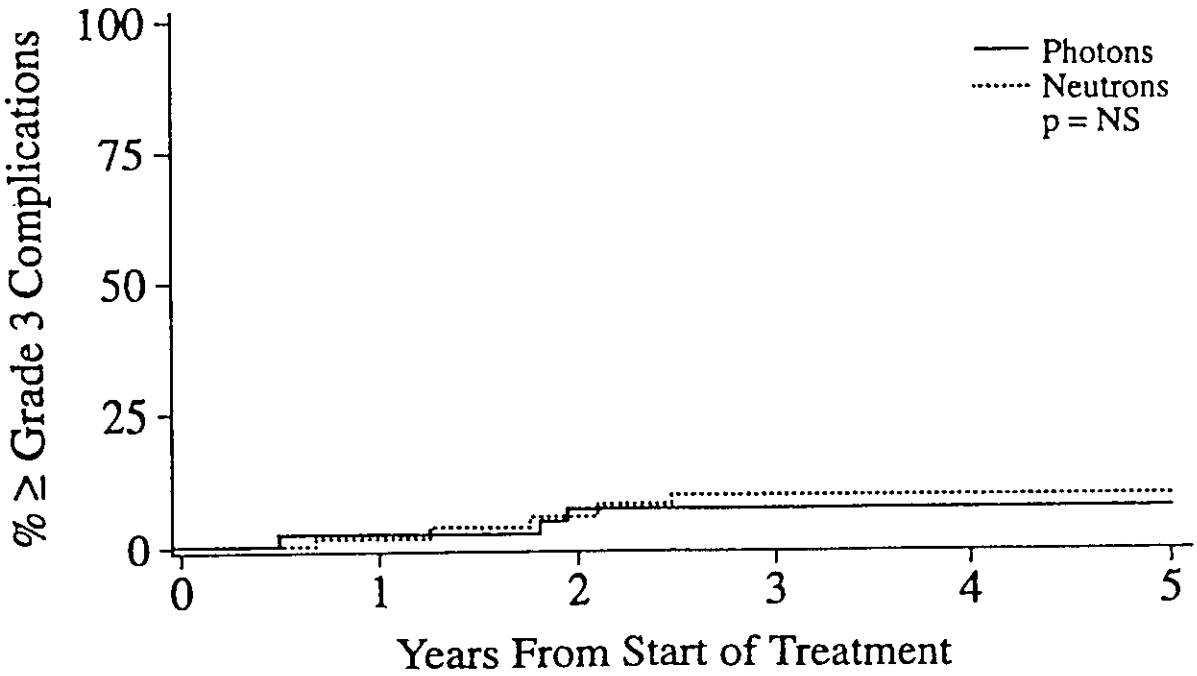

% ≥ Grade 3 Complications
100
75
50
25
0
0
1
2
3
4
5
Years From Start of Treatment
Photons
Neutrons
p = NS

Fig 4b

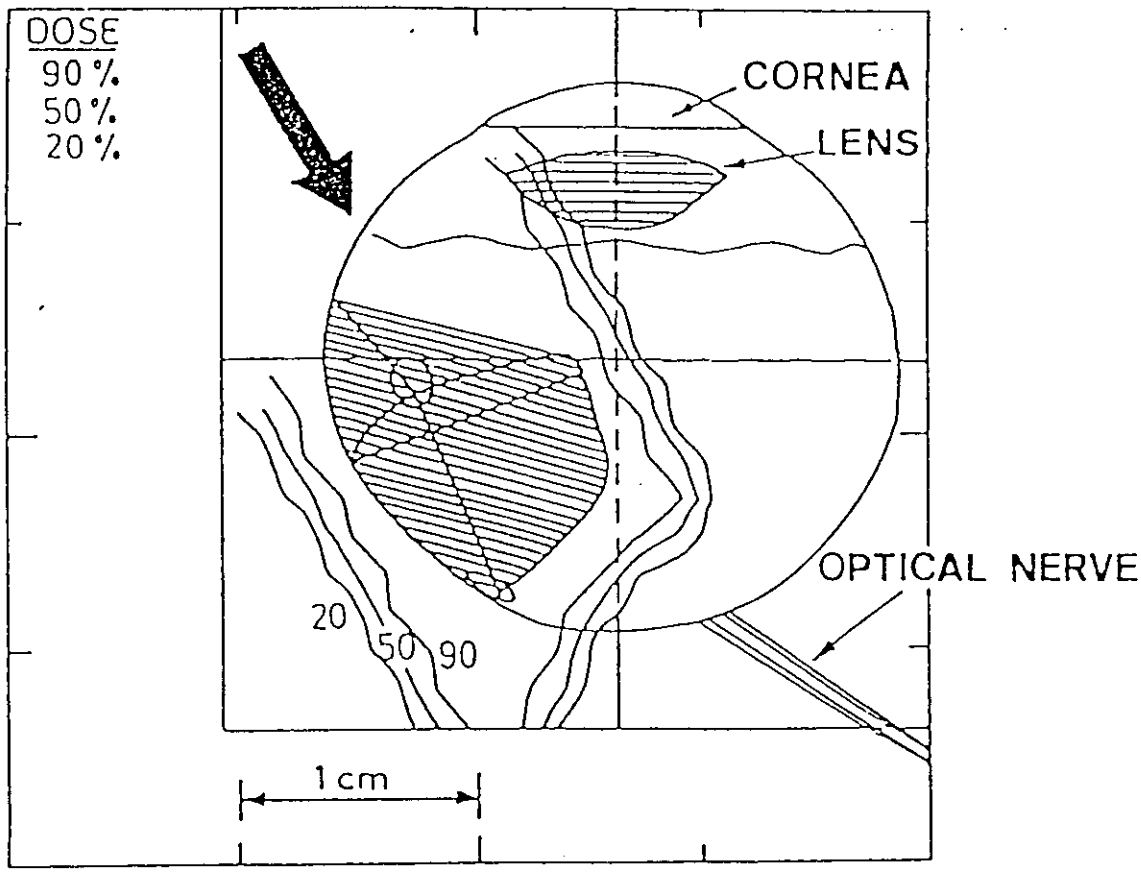


Figure 5

Proton therapy for uveal melanoma. Dose distribution obtained with a beam of 60 MeV protons with a spread-out Bragg peak (energy modulated from 14-60 MeV). Transverse section through the centre of the eye. The position of the tumour is indicated by shading. Irradiation with protons gives a homogeneous dose to the tumour with maximum sparing of the normal tissues, but extreme precision is needed when positioning the patient.

(redrawn from [6]).

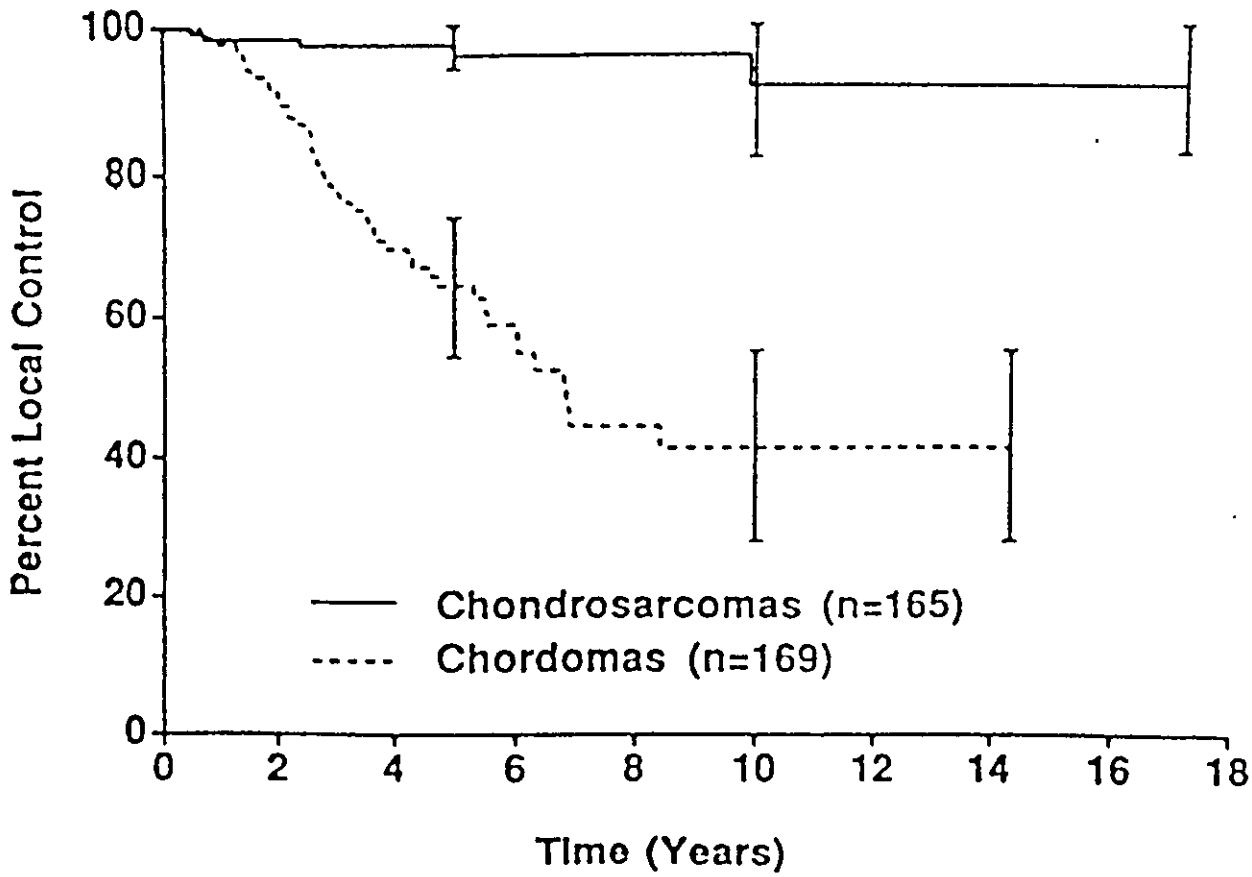


Figure 6

Proton beam therapy of tumours of the base of skull.

6.a. Probability of local control in patients with chordomas (169) and low-grade chondrosarcomas (165) of the skull base.

6.b. Probability of survival after relapse in skull base and cervical spine chordoma patients who received salvage therapy (49 patients) or supportive case only (14 patients).

(from Munzenrider and Liebsch, [13]).

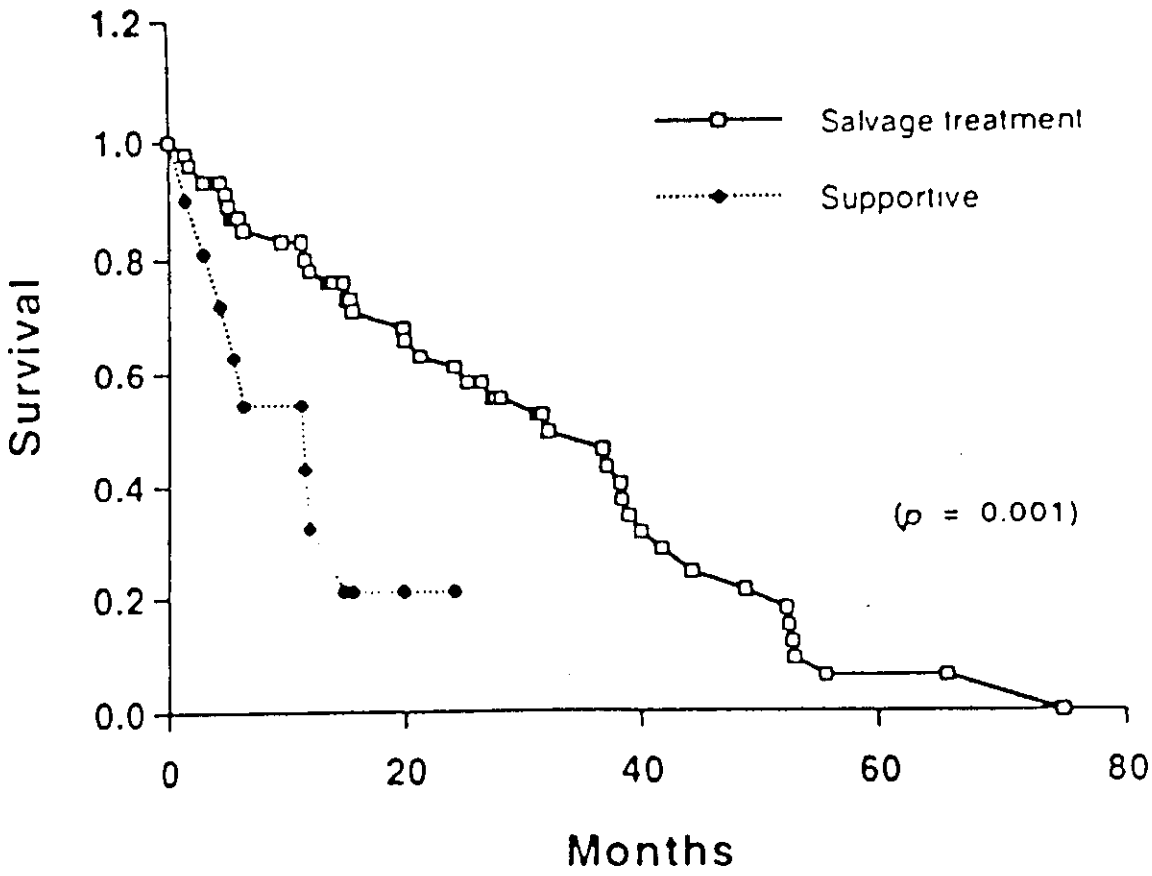

1.2
1.0
0.8
0.6
0.4
0.2
0.0
Survival
0
20
40
60
80
Months
Salvage treatment
Supportive
(p = 0.001)

Fig 6 e

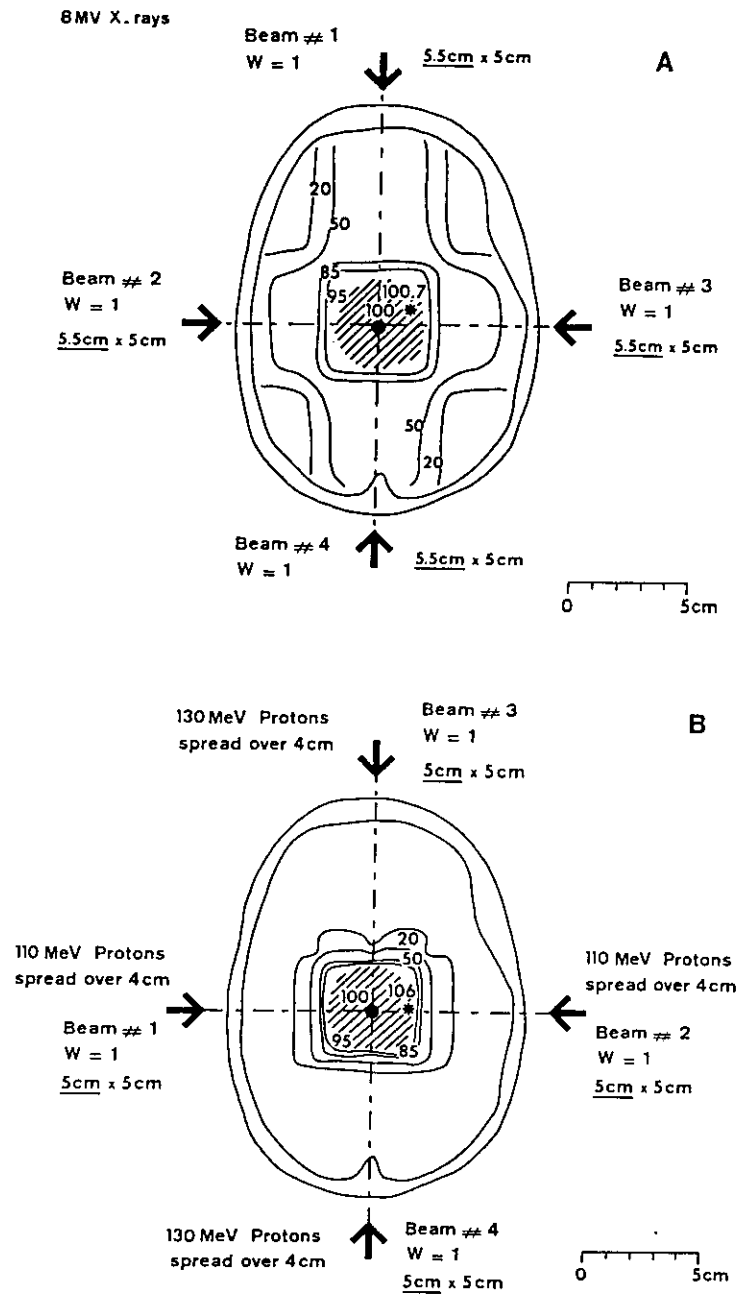


Figure 7

Treatment of a craniopharyngioma in a child: comparison of dose distributions for photons and protons.
Typical planning sections for a large suprasellar craniopharyngioma, in a 3 year old child, treated with photons (a) or protons (b). The target volume is indicated by the hatched area. For photons and protons, four equally weighted beams were used and the normalization point was chosen at the intersection of the beams axes. For the 4 proton beams, the Bragg peak was spread over 4 cm [15].

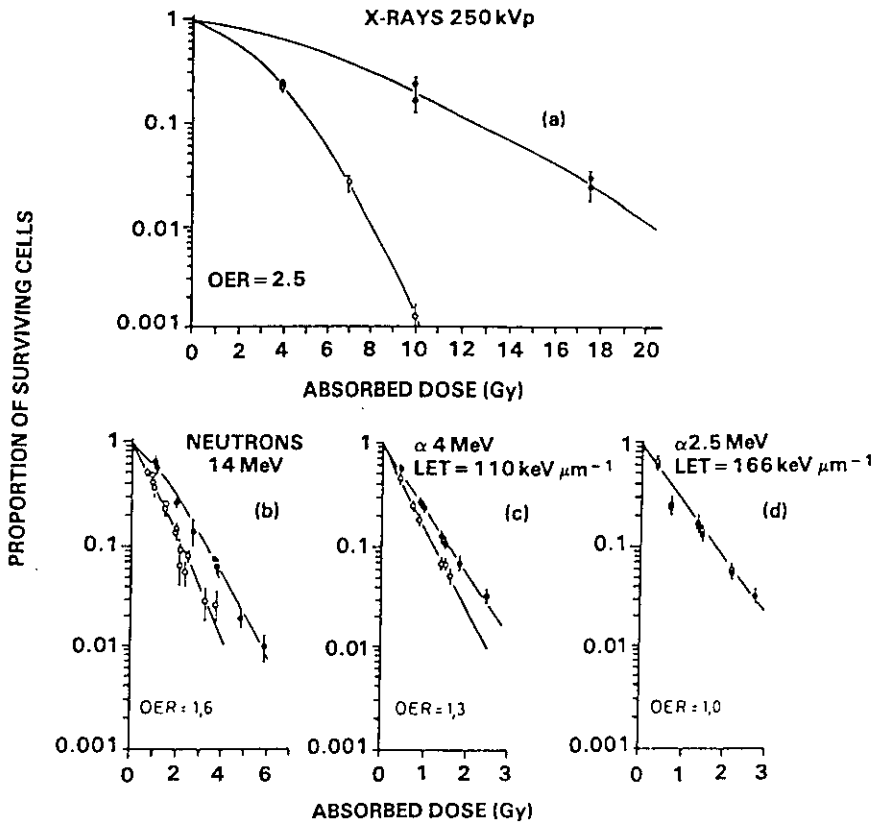


Figure 11.5. Survival curves of human kidney cells T1 irradiated under hypoxic and aerobic conditions with different qualities of radiation.
(a) 250 kV X-rays (LET about 1·3 keV μm^{-1});
(b) 14 MeV neutrons produced by the (d,T) reaction (LET about 12 keV μm^{-1});
(c) 4 MeV α-particles (LET = 110 keV μm^{-1});
(d) 2·5 MeV α-particles (LET = 166 keV μm^{-1}).
After [1, 10].

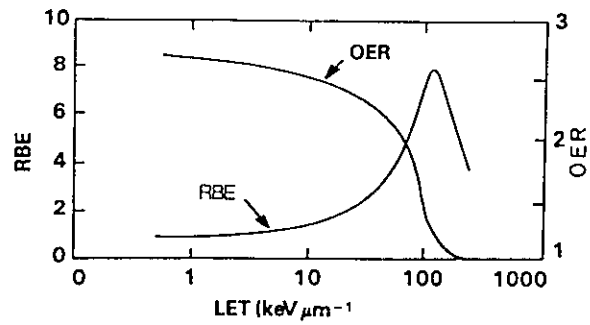


Figure 11.6. Variation of RBE (Figure 11.4) and OER (Figure 11.5) as a function of LET. The curves vary inversely and the most rapid changes occur at about 100 keV μm^{-1}.
After [3].

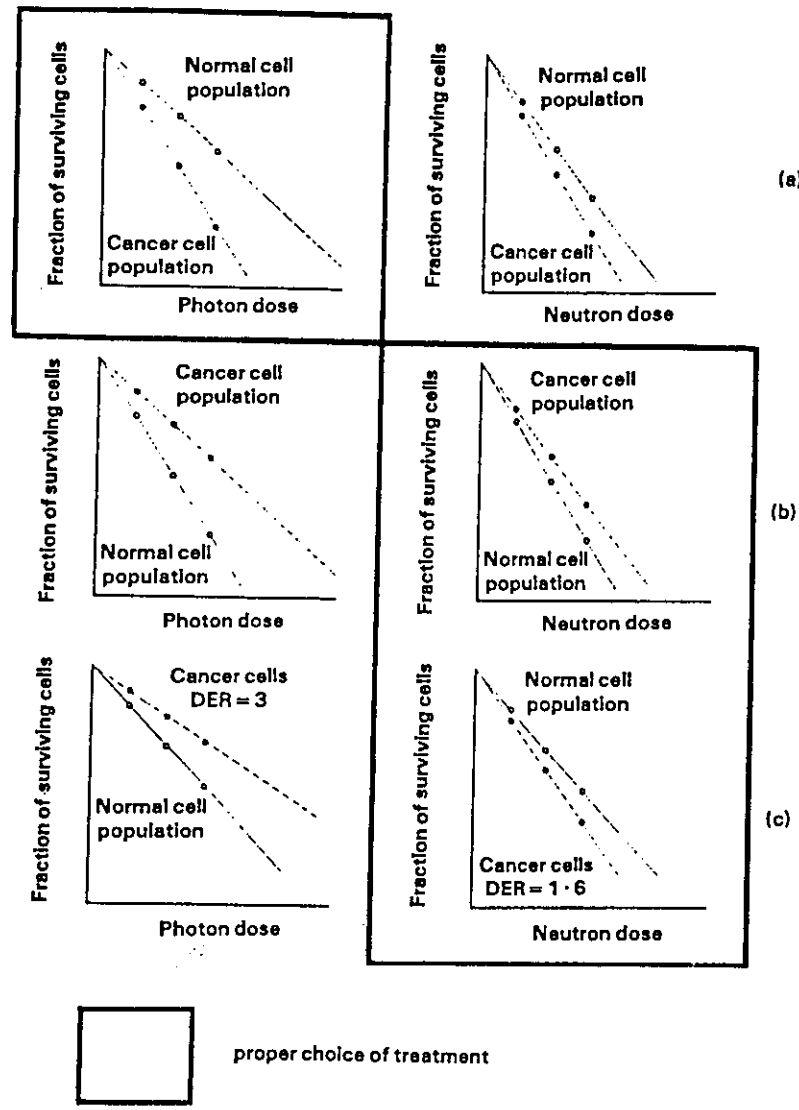
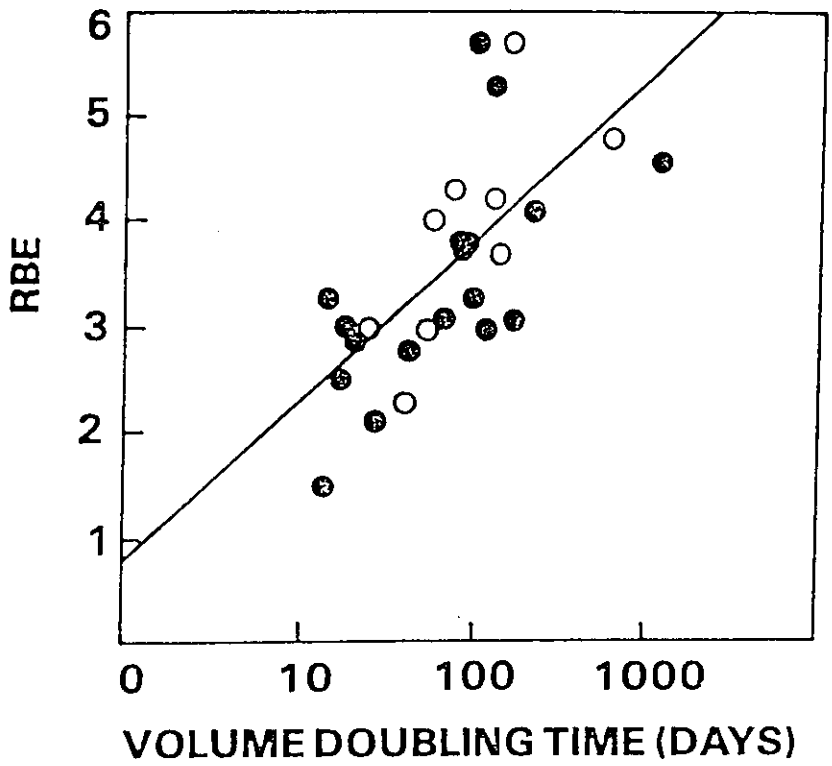


Figure 11.15. Importance of patient selection for fast neutron therapy. Three possible clinical situations are considered.
In the first (a), the cancer cells are more sensitive to X-rays than the critical normal cell population, and there is no argument at all for using neutrons which would reduce a favourable differential effect.
In the second situation (b), neutrons bring a benefit by reducing a difference in radiosensitivity which would selectively protect the cancer cell population.
A third more favourable situation is shown (c) where the relative radiosensitivities are reversed (see text and Figure 11.14). It has been assumed in the figure that the survival curves are exponential after fractionated irradiation, i.e. a constant proportion of the cells is killed at each session. However, the exact shape of the cell survival curve is not essential for the present discussion.



3. Relation between the RBE of neutrons for regression of lung metasta eir doubling time. •, Measured values of RBE; ○, values estimated from eutrons only. For the 15 MeV neutrons used in this study (produced by he RBE for tolerance of the most important normal tissues is about 3. e therefore a good indication (RBE > 3) for tumours having doubling t n 100 days.

Proton therapy for uveal melanoma
John E. Munzenrider, Innsbruck, 1998

Local control:

5 years	(236 patients)	96.3 + 1.5 %
7	(82)	95.4 + 3.3 %

Failures:
2 after 4 years
2 in the treated volume
10 in the margin

Survival: 80 % at 5 years (similar to enucleation)

Eye retention:

small tumours	97 %
intermediate t.	93 %
large tumours	78 %

(>8 mm in height, >16 mm in diameter, involvement of ciliary body, distance between posteriot tumour edge and fovea)

Helium ions vs 125-iodine plaque brachytherapy for uveal melanoma.
John.E.Munzenrider,InnsbrucK, 1998

Randomized trial (UCSF-LBerkeleyVL)
<10 mm in height, <15 mm in diameter

Randomize: *70 Gy/5 F helium ions
*70 Gy to the tumour apex with 125-iodine episcleral plaque

Local control (initial report): He 100 %
125-I 87 %

Enucleation rate higher for iodine
Anterior segment complication rate higher for He

Tumours of the skull base

J.E.Munzenrider and N.J.Liebsch, Innsbruck, 1998

Skull base 3 %
Cervical spine 11 % of primary bone tumours.

---

519 patients with skull base tumour
290 chordomas
229 low grade chondrosarcomas

Initial symptomes: headache and intermittant diplopia

Local recurrence free survival (LRFS):

at 5 years: 98 % for chondrosarcomas
73 % for chordomas
at 10 years: 94 % for chondrosarcomas
54 % for cordomas

for chordomas
at 5 years
for males LRFS 81 % vs 65 % for females
at 10 years
for males 65 % vs 42 for females
(no difference for chondrosarcomas)

Overall survival:

at 5 years: 91 % for chondrosarcomas
80 % for chordomas
at 10 years: 88 % for chondrosarcomas
54 % for cordomas

Salvage treatment

Survival at 2 years 63 % (supportive therapy only 21 %)
5 7 %

The future of fast neutron (high-LET) therapy (?)

1)
Past experience in neutron therapy has shown the usefulness of high-LET radiations for

- -salivary gland tumours
- -prostatic adenocarconomas
- -some other selected groups of patients (not definitely proven by randomized trials)

in general, slowly growing, well differentiaded tumours, hypoxic, etc...
(therapeutic gain even in suboptimal conditions)

2)
Importance of patient selection
radiobiological arguments
(hypoxia, cellular radiosens., kinetics, etc)

3)
Patient recruitement
(10-20 % of all radiotherapy patients)

4)
Importance of technical problems

The radiobiological gain does not compensate for "poor" technical conditions
(i.e.,one of the lessons of neutron therapy!!)

(a) physics machine (?)
(b) hospital based (dedicated) machine

=conventional technology (cf protons)
=supraconducting machines

(c) depth-doses, skin sparing, penumbra, isocentric gantry, multileaf collimator, etc

5)..and heavy ions ?...

radiobiological advantage + physical selectivity

Neutron experience has shown the benefit of high-LET radiations, i.e. the justification of heavy ions (compared to protons).
Justification of the costs ?

The future for high-LET radiation therapy??

-dedicated heavy-ion therapy machine
(Chiba, GSI, Heidelberg, Med-AUSTRON, etc),

-as an alternative (at lower cost?), the progress made in photon therapy should help to improve the physical selectivity of fast neutrons (multileaf, patient positioning, 3-D treatment planning, even IMRT, etc.).

This is the "sine qua non" condition for survival of neutron therapy.